UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,664	12/05/2003	Hidenobu Yaku	2003-1763A	5974

513 7590 09/25/2006

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,664	YAKU ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *23-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/05/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 6/29/2006. Currently Claims 1-36 are pending. Claims 23-36 are withdrawn.

2. The following rejections are necessitated by amendment. Response to arguments follows.

3. This action is FINAL.

Priority

4. Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Japan on 12/06/2002 and 08/07/2002. It is noted, however, that applicant has not filed certified translated copies of the 2002-355915 and 2003-288707 applications. Therefore, priority to the 2002-355915 and 2003-288707 applications has not been granted to the instantly pending claims.

Response to Arguments

The reply asserts that certified copies of the untranslated foreign priority documents have been submitted and that the MPEP only requires certified translations of the priority documents only to establish priority to overcome a prior art rejection over intervening art (p. 1 last paragraph and p. 2 1st paragraph). This argument has been

thoroughly reviewed but is not found persuasive. 35 USC 119 Benefit of earlier filing date; right of priority (b)(3) states:

> (3) The Director may require a certified copy of the original foreign application, specification, and drawings upon which it is based, a translation if not in the English language, and such other information as the Director considers necessary. Any such certification shall be made by the foreign intellectual property authority in which the foreign application was filed and show the date of the application and of the filing of the specification and other papers.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Information Disclosure Statement

Response to Arguments

The reply asserts that reference AH and AK have not been considered (p. 13 Part III 2nd paragraph). Reference AK was not originally considered because no translation of any part of the reference was provided. A translation of reference AK has been provided with the office action mailed 2/15/2006, therefore, the reference has now been considered since there is a translation on the record for the case. Reference AH does not have a translation of any part of the reference, therefore, it is still not considered.

Terminal Disclaimer

5. The terminal disclaimer filed on 6/15/2006 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US Patent Applications 11/180881 and 10/699848 has been reviewed and is accepted.

The terminal disclaimer has been recorded. The obviousness double patent rejections have been withdrawn in view of the Terminal Disclaimer.

Withdrawn Rejections

6. The rejection of Claims 1-22 under 35 USC 112/second paragraph made in section 9 of the previous office action, is moot in view of the amendments to the Claims. Specifically the amendment that clarifies the nucleotide position at the 3' terminal.

7. The rejection of Claims 1-6, 9, 20, and 21 under 35 USC 103(a) made in section 12 of the previous office action, is moot in view of the amendments to the Claims. Specifically the amendment that clarifies the nucleotide position at the 3' terminal.

8. The rejection of Claims 7-8 under 35 USC 103(a) made in section 13 of the previous office action, is moot in view of the amendments to the Claims. Specifically the amendment that clarifies the nucleotide position at the 3' terminal.

9. The rejection of Claim 22 under 35 USC 103(a) made in section 14 of the previous office action, is moot in view of the amendments to the Claims. Specifically the amendment that clarifies the nucleotide position at the 3' terminal.

10. The rejection of Claims 14-19 under 35 USC 103(a) made in section 15 of the previous office action, is moot in view of the amendments to the Claims. Specifically the amendment that clarifies the nucleotide position at the 3' terminal.

New Matter in Specification

11. The amendment filed 6/29/2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is as follows: pages 1-21 describing 5 specific experiments with specific primer sequences, target sequences, and results and pages 1-2 with Figures 1-3.

Applicant is required to cancel the new matter in the reply to this Office Action.

132 Declaration

The declaration under 37 CFR 1.132 filed 6/29/2006 has been thoroughly reviewed but has been found to be insufficient to provide unexpected results support to the current claims. When all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

The declaration asserts 5 experiments were performed. Experiment 1: The declaration asserts that there were two target sequences (p. 1 lines 10-20). The declaration asserts that these sequences differed at the last nucleotide (C/T) (p. 1 lines

11 and 15). The declaration asserts that 8 primers were used with differing mismatches at the 3' end (p. 2 lines 8-15). The declaration asserts a specific PCR reaction with the specific primers was performed with Target Sequence 1. Figure 1 shows the results that less of the primers amplified with Target 1 with the specific primers 1-4-1-8.

Experiment 2: The declaration asserts Target sequence 1 and 3 differed at the last nucleotide (C/A) (p. 5 lines 10-12). The declaration asserts 8 primers were used (these primers differed from the first set of primers at the last nucleotide of the 3' end) (p. 6 lines 3-10). The declaration asserts a specific PCR reaction with the specific primers was performed with Target Sequence 1. Figure 2 shows the results that less of the primers amplified with Target 1 with the specific primers 2-4-2-8.

Experiments 3-5 followed the same pattern as Experiment 1, except the target and probes were designed based on other nucleotide regions of the lambda DNA.

These experiments are insufficient to provide unexpected results because the claims are not limited to the specific method using the specific primers presented in the declaration. The claims are not limited to the specific primers with mismatches at only the 2 and 3 nucleotide position. Further, the claims are not limited to the reaction conditions needed to obtain the results presented in the declaration. The declaration indicates a method in which primers that have more mismatches on the 3' end anneal less to targets compared to primers with only one mismatch at the 3' end, but the claims are drawn to any number of mismatches. The claims are not commensurate in scope with the method steps presented by the declaration and therefore the declaration is insufficient to overcome obviousness rejections.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-9 and 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93).

With Regard to Claim 1, Zhou et al. teaches a method of detection of single nucleotide polymorphisms (SNPs) in a target (determining a base type) (Abstract). With regard to Claim 1a, Zhou et al. teaches a reaction solution comprising a target, SNP primers, theromostable DNA polymerase, and dNTPs (p. 4 1st column Allele-specific extension reaction). With regard to Claim 1b, Zhou et al. teaches hybridization of the primer to the target and determination of a SNP (Figure 2 p. 4). With regard to Claim 1c, Zhou et al. teaches detecting luminescence when the primer is extended (degree of progress (Figure 2 p. 4).

Claim 1 is drawn to an uncomplimentary region, which is adjacent to the substitution region and consists of two bases which are located in the second and third positions and is uncomplimentary to the target strand. The claim defines the region as

uncomplimentary to the target. Because the claim defines the region as uncomplimentary, the claim is interpreted to encompass an uncomplimentary at either the 2nd or 3rd position. Zhou et al. teaches a primer which is uncomplimentary at the third position and therefore covers all the limitations of the claim. Zhou et al. teaches there is a complementary region adjacent to the uncomplimentary region (Figure 2 p. 4).

With regard to Claim 2, Zhou et al. teaches using a thermostable DNA polymerase without exonuclease activity (p. 4 1st column Allele-specific extension reaction).

With regard to Claim 3, Zhou et al. teaches the primer and the target are DNA (Abstract).

With regard to Claim 4, Zhou et al. teaches performing a PCR reaction with a forward and reverse primer (p. 4 1st paragraph).

With regard to Claim 5, Zhou et al. teaches the base difference is determined by the extension of the primer wherein no extension provides no measurable luminescence (Figure 2 p. 4).

With regard to Claim 6, Zhou et al. teaches the SNP typing can be performed by measuring pyrophosphate or by gel-based electrophoresis (Table 2 p. 9).

With regard to Claim 7, Zhou et al. teaches measuring pyrophosphate (Ppi) (Abstract). With regard to Claim 8, Zhou et al. teaches measuring the amount of Ppi generated (Figure 1). With regard to Claim 9, Zhou et al. teaches determination of the SNP (base sequence determination) and determining if the SNP is an A, G, C, or T (base type) (Figure 3 p. 5).

With regard to Claims 20 and 21, Zhou et al. teaches a method in which 16 SNPs are detected with varying size of primers (Table 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Scopes et al.

(Analytical Biochemistry 1972 Vol. 49 p. 88) and Benkoel et al. (The Journal of Histochemistry and Cytochemistry 1976 Vol. 24 p. 1194).

Zhou et al. teaches a method of detection of single nucleotide polymorphisms (SNPs) in a target (determining a base type) (Abstract). Zhou et al. teaches a reaction solution comprising a target, SNP primers, theromostable DNA polymerase, and dNTPs (p. 4 1st column Allele-specific extension reaction). Zhou et al. teaches hybridization of the primer to the target and determination of a SNP (Figure 2 p. 4). Zhou et al. teaches detecting luminescence when the primer is extended (degree of progress (Figure 2 p. 4). With regard to Claim 13, Zhou et al. teaches reduction of residual Ppi by reaction of Ppase in the sample (conversion to inorganic phosphoric acid by reaction of pyrophosphatase in sample (p. 7 2nd column 1st two paragraphs).

Zhou et al. teaches measuring ppi, however, Zhou et al. does not teach the steps of converting pyrophosphoric acid into inorganic phosphoric acid.

With regard to Claim 10, Scopes et al. teaches a method of detecting the conversion of organic phosphate into inorganic phosphate (p. 88 1st paragraph). Scopes et al. teaches a method of using glyceraldehydes-3-phosphate (p. 88 1st chemical formula). Scopes et al. teaches this gets converted into 1,3-diphosphoglycerate concomitant with the reduction of coenzyme to NADH (nicotinamide adenine dinucleotide) (p. 88). Scopes et al. teaches providing glyceraldehydes 3-phosphatedehyrogenase (p. 89 1st paragraph).

With regard to Claims 10 and 11, Benkoel et al. teaches using ferricyanide as an electron acceptor (Abstract). With regard to Claim 12, Benkoel et al. teaches

determining the prices localization of various reactions in different electron transfer chains determined by using different ferricyanide concentrations and intermediate electron carriers such as diaphorase (Abstract).

Therefore it would have been prima facie obvious to one of skill in the art at the time of the invention to modify the method of Zhou et al. to incorporate the method steps of pyrophosphoric conversion as taught by Scopes et al. and Benkoel et al. The ordinary artisan would have been motivated to incorporate the method steps of pyrophosphoric acid conversion as taught by Scopes et al. and Benkoel et al. in order to maximize the detection of the SNPs in the reaction. Scopes et al. teaches a rapid detection of phosphate liberation in samples (p. 88 last paragraph). The skilled artisan would be motivated to use the steps as taught by Scopes et al. to quickly detect the conversion of inorganic phosphorus in a sample. Further, Benkoel et al. teaches using copper ferrocyanide to observe electron transfer without staining (p. 11944 1st paragraph). The skilled artisan would be motivated to use both ferrocyanide and diaphorase to determine the precise localization of reactions (Abstract).

1. Claims 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Bille et al. (herein referred to as Bille, 1992, Phys. Plantarum, vol. 84, pages 250-254).

Zhou et al. teaches a method of detection of single nucleotide polymorphisms (SNPs) in a target (determining a base type) (Abstract). Zhou et al. teaches a reaction

solution comprising a target, SNP primers, theromostable DNA polymerase, and dNTPs (p. 4 1st column Allele-specific extension reaction). Zhou et al. teaches hybridization of the primer to the target and determination of a SNP (Figure 2 p. 4). Zhou et al. teaches detecting luminescence when the primer is extended (degree of progress (Figure 2 p. 4).

Zhou et al., however, does not teach measurement of pyrophosphate *specifically* where the pyrophosphate is detected by applying part of the amplification reaction to a membrane system that contains pyrophosphatase and measuring the change in H+ concentration.

Bille teaches that a quantitative relationship can be obtained between pyrophosphate concentration and a change in pH inside a vesicle membrane that contains H+-pyrophosphatase when pyrophosphate is added to a system containing vesicle membranes (claims 14, 15, and 19, see page 251, column 1, all of para 4, page 252, column 2 all of para 1, and Figures 2 and 3 of Bille). Bille teaches that the change in pH in this system is measured by a change in the absorbance of acridine orange (claims 16 and 17, see page 251, column 1, all of para 4, page 252, column 2 all of para 1, and Figures 2 and 3 of Bille). Bille also teaches that a positive current into a vacuole containing pyrophosphatase caused by a change in pH can be detected upon addition of pyrophosphate to vacuoles by the patch-clamp technique (claim 18; see page 252, column 2, all of para 4, page 253, column 1, all of para 1, and Figure 6 of Bille).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of detecting pyrophosphate

in SNP detection of Zhou et al. by subjecting the pyrophosphate to the system of vesicle membranes having pyrophosphatase and measuring the change in pH inside the vesicles or detecting such a pH change by the patch-clamp technique in view of the teachings of Bille for the purpose of developing a sensitive method of pyrophosphate detection in SNPs as taught by Zhou et al. The ordinary artisan would have a reasonable expectation of success that using the membrane associated pyrophosphatase system with a pH sensitive dye or path-clamp method taught by Bille to measure pyrophosphate levels in the SNP detection of Zhou et al. would result in a sensitive and effective measurement of pyrophosphate, as evidenced by Figures 3 and 6 of Bille, released during the extension reaction in the method taught by Zhou et al. because Bille teaches a direct quantitative relationship between pyrophosphate levels and resulting pH change in vesicle membranes as measured by a pH sensitive dye or the patch-clamp technique.

15. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou et al. (Nucleic Acids Research 2001 Vol. 29 p. e93) in view of Newton (US Patent 5525494, 06/1996).

Zhou et al. teaches a method of detection of single nucleotide polymorphisms (SNPs) in a target (determining a base type) (Abstract). Zhou et al. teaches a reaction solution comprising a target, SNP primers, theromostable DNA polymerase, and dNTPs (p. 4 1st column Allele-specific extension reaction). Zhou et al. teaches hybridization of

the primer to the target and determination of a SNP (Figure 2 p. 4). Zhou et al. teaches detecting luminescence when the primer is extended (degree of progress (Figure 2 p. 4). Zhou et al. teaches a method in which 16 SNPs are detected with varying size of primers (Table 2).

Zhou et al., however, does not teach specifically labeling the primers with respective fluorenscences which are different in wavelength.

Newton teaches that allele specific amplification can be conveniently effected by labeling the primers with different fluorescent labels such as fluoroscein (green) and rhodamine (red) to allow the detection of homo- and heterozymgotes by color blending (see column 4, lines 54-64 of Newton).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of mutation detection taught by Zhou et al. by labeling the primers used for primer extension with different fluorescent labels such as fluoroscein (green) and rhodamine (red) to allow the detection of homo- and heterozygotes by color blending in view of the teachings of Newton. The ordinary artisan would have been motivated to improve the method of mutation detection taught by Zhou et al. by labeling the primers used for primer extension with different fluorescent labels such as fluoroscein (green) and rhodamine (red) to allow the detection of homo- and heterozygotes by color blending because Newton teaches that this labeling method allows for convenient detection of mutations by allele specific amplification.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

BJ FORMAN, PH.D.
PRIMARY EXAMINER